Best Practice

STRAIGHT TO THE POINT

Generalized anxiety and panic disorder

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INTRODUCTION

- Primary care physicians should be able to recognize and treat basic anxiety disorders. Among the anxiety disorders listed by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* are generalized anxiety disorder, anxiety due to a general medical condition, panic disorder with and without agoraphobia, and substance-induced anxiety disorder
- Anxiety disorders best referred to a psychiatrist include agoraphobia without panic disorder, specific and social phobias, obsessive-compulsive disorder, post-traumatic stress disorder, and acute stress disorder
- Anxiety may present as insomnia, headaches, ongoing fears, musculoskeletal pain, or gastrointestinal disturbance

The etymology of *anxiety*

The term stems from the Greek *angho* (ανχθ): "to squeeze, embrace, or throttle." The meaning evolved to "weighed down with grief, burdens, trouble" and concurrently to the Latin *anxietas*: "troubled in mind."

GENERALIZED ANXIETY DISORDER

Epidemiology

- The lifetime prevalence of generalized anxiety disorder (GAD) is 5.1%. The 1-year prevalence is 3.1%[1]
- Women are affected about 1.9 times as often as men[1]
- GAD is frequently associated with mood disorders, other anxiety disorders, and substance abuse

Treatment

- Initial therapy may consist of the administration of a benzodiazepine for 2 to 6 weeks or buspirone hydrochloride for several months
- Antidepressant medications need to be taken 3 to 4 weeks before the onset of action. If used, they are often initially paired with a benzodiazepine
- Cognitive therapy is also effective for GAD; it may be better than pharmacotherapy. The combination of cognitive therapy and medication improves outcome over treatment with medication alone[2]
- There is no well-designed study of the long-term treatment of GAD[3]

Buspirone

- Among patients with GAD who take buspirone, 54% have significant clinical improvement compared with 28% of patients who take placebo[4]
- Buspirone and benzodiazepines have similar efficacy[5]

[1] *Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Study. Arch Gen Psychiatry 1994;51:8-19.*

[2] *Barkovec TD, Whisman MA. Psychosocial treatment for generalized anxiety disorder. In: Mavissakalian MR, Prien RF, eds. Long-Term Treatments of Anxiety Disorders. Washington, DC: American Psychiatric Press; 1996:171-200.* A review of 11 randomized controlled trials (RCTs) of the treatment of GAD.

[3] *Mahe V, Balogh A. Long-term pharmacological treatment of generalized anxiety disorder. Int Clin Psychopharmacol 2000;15:99-105.*

[4] *Gammans RE, Stringfellow JC, Hvizdos AJ, et al. Use of buspirone in patients with generalized anxiety disorder and coexisting depressive symptoms: a meta-analysis of eight randomized, controlled studies. Neuropsychobiology 1992;25:193-201.* A meta-analysis of 520 patients in eight double-blind RCTs that assessed the use of buspirone versus placebo.

[5] *Pecknold JC, Matas M, Howarth BG, et al. Evaluation of buspirone as an antianxiety agent: buspirone and diazepam versus placebo. Can J Psychiatry 1989;34:766-771.* A double-blind RCT of 119 outpatients who had GAD.

- Buspirone is effective only if taken regularly
- Adverse effects—headache, nausea, and dizziness—are mild and infrequent. Unlike benzodiazepines, buspirone does not impair memory, cognitive performance, or driving skills. It has no sedative-hypnotic effects
- Buspirone has no potential for dependence, withdrawal symptoms, or rebound anxiety after drug withdrawal
- In one observational study, buspirone was shown to be safe to use for as long as 1 year[6]
- Probably less relapse occurs after buspirone treatment than after treatment with benzodiazepines

[6] *Rakel RE. Long-term buspirone therapy for chronic anxiety: a multicenter international study to determine safety. South Med J 1990;83:194-198.* The study compared 264 patients treated for 6 months with 424 patients treated for 12 months.

Benzodiazepines

- Benzodiazepines are effective, but long-term use carries the risk of dependence and occasionally addiction
- The longer-acting agents are least likely to cause dependence. These include chlordiazepoxide hydrochloride, diazepam, and flurazepam hydrochloride
- Side effects include sedation, impairment of performance, transient anterograde amnesia, disinhibition, and depression
- These agents should be used with caution in patients with a history of substance abuse because of the risk of central nervous system depression and addiction
- Withdrawal seizures are most likely with short-acting benzodiazepines
- Benzodiazepines alone rarely cause fatal overdose, but when combined with other central nervous system depressants, they can be lethal

Buspirone vs benzodiazepines vs placebo for anxiety over 4 weeks: Hamilton Anxiety Scale (HAM-A) ratings[5]

Agent	HAM-A total score Week 0	Week 2	Week 4
Buspirone	24.5	14.3	12.1
Diazepam	25.5	13.5	13.3
Placebo	24.5	18.9	17.2

The Hamilton Anxiety Scale

The Hamilton Anxiety Scale, often used in clinical trials, contains 14 symptoms (7 psychic and 7 somatic), each rated from 0 to 4 points for severity. The maximum score for the psychic and somatic sections is 28 each, and the maximum combined score is 56. The average person has a total score of less than 5; a score of 15 represents clinically significant anxiety.

Antidepressant drugs

- Several studies have shown benefit with the use of antidepressant medications, particularly imipramine hydrochloride, in generalized anxiety disorder. Although benzodiazepines provide greater relief of symptoms during the first 2 weeks of study, antidepressants show equal or better relief thereafter

*Antidepressants vs benzodiazepines vs placebo for anxiety over 8 weeks: Hamilton Anxiety Scale (HAM-A) ratings**

Agent	HAM-A psychic score Week 1	Week 4	Week 8
Imipramine	21.1	12.7	10.8
Trazodone	21.4	14.3	12.9
Diazepam	17.5	14.0	13.0
Placebo	21.7	18.5	16.0

*From Rickels et al.[7]

[7] *Rickels K, Downing R, Schweizer E, Hassman H. Antidepressants for the treatment of generalized anxiety disorder: a placebo-controlled comparison of imipramine, trazodone, and diazepam. Arch Gen Psychiatry 1993;50:884-895.* An RCT of 231 patients who had a Hamilton scale score of 18 or higher. Mean maximal daily dose for each drug: imipramine, 143 mg; trazodone hydrochloride, 255 mg; and diazepam, 26 mg.

Botanicals: kava extract

- Kava extract is superior to placebo for the treatment of anxiety; it lowers anxiety by a mean of 10 points more than placebo on the HAM-A scale[8]

[8] *Pittler MH, Ernst E. Efficacy of kava extract for treating anxiety: systematic review and meta-analysis. J Clin Psychopharmacol 2000;20:84-89.* A meta-analysis of 198 patients in 3 double-blind RCTs.

Referral to a psychiatrist, psychologist, or therapist

- Consider referral for any patient who wants cognitive therapy
- Patients refractory to medical therapy or with recurrent relapse after withdrawal of therapy should be referred to a psychiatrist

PANIC DISORDER

Epidemiology

- The lifetime risk of having an isolated panic attack is 7.2%[9]
- The lifetime and 1-year prevalence of panic disorder is 3.5% and 2.3%, respectively[1]
- The lifetime risk is about 2.5 times greater in women[1]
- In primary care settings, the prevalence is 6.5% to 19%[10]
- As many as 25% of first-degree relatives of patients with panic disorder have the disorder themselves[10]
- The prevalence of panic disorder in patients with chest pain who have normal findings on coronary angiography is 33% to 43%[10]
- The rate of suicide attempts in patients with panic disorder is 7%; in patients with panic disorder and depression, the rate is 20%[10]

[9] *Kessler RC, Stang PE, Wittchen HU, Ustun TB, Roy-Burne PP, Walters EE. Lifetime panic-depression comorbidity in the National Comorbidity Survey. Arch Gen Psychiatry 1998;55:801-818.*

[10] *Pary R, Lewis S. Identifying and treating patients with panic attacks. Am Fam Physician 1992;46:841-848.*

DSM-IV criteria for generalized anxiety disorder

- There must have been a period of at least 6 months with prominent tension, worry, and feelings of apprehension about everyday events and problems
- At least four of the symptoms listed below must be present, and at least one must be from each group
  1. *Autonomic arousal symptoms:* palpitations, sweating, trembling or shaking, or dry mouth
  2. *Symptoms involving chest and abdomen:* difficulty breathing, feeling of choking, chest pain or discomfort, nausea or abdominal distress
  3. *Symptoms involving mental state:* feeling dizzy or light-headed, derealization, depersonalization, fear of losing control or going crazy, fear of dying
  4. *General symptoms:* hot flushes or cold chills, numbness or tingling sensations
  5. *Symptoms of tension:* muscle tension or aches and pains; restlessness and inability to relax; feeling keyed up, on edge, or mentally tense; a sensation of a lump in the throat or difficulty in swallowing
  6. *Other nonspecific symptoms:* exaggerated response to minor surprises, difficulty concentrating because of worrying, persistent irritability, difficulty getting to sleep because of worrying
- The patient does not meet the criteria for panic disorder, phobic anxiety disorder, obsessive compulsive disorder, or hypochondriacal disorder
- The anxiety is not due to a physical disorder, an organic mental disorder, or a psychoactive substance-related disorder

DSM-IV criteria for panic disorder

Panic attack is described as a sudden discrete period (usually 5-30 minutes) of intense fear or discomfort accompanied by at least four symptoms from groups 1 to 4 of the generalized anxiety disorder symptoms. At least one symptom must be from group 1.

Panic disorder is the presence of recurrent unexpected panic attacks followed by at least 1 month of persistent concern about having another panic attack, worry about the possible implications or consequences of the panic attacks (anticipatory anxiety), or significant behavioral change related to the attacks (including agoraphobia or social phobia).

The panics of Charles Darwin

At the age of 28, Darwin notes, "I have awakened in the night being slightly so unwell and felt so much afraid though my reason was laughing and told me there was nothing." *Barloon TJ, Noyes R Jr. Charles Darwin and panic disorder. JAMA 1997;277:138-*

Diagnosis

- Onset generally occurs between ages 15 and 30 years
- Patients must have four panic attacks in 1 month or one attack with persistent fear

- Panic disorder is easily missed. The average patient who has panic disorder sees 10 physicians before being diagnosed. This may be due to the often misleading presentation of anxiety disorder: chest pain, shortness of breath, gastrointestinal symptoms, and neurologic symptoms[10]
- Common comorbidities include major depression, agoraphobia, and substance abuse. Depression coexists in more than 50% of patients with panic attack or panic disorder[9]
- Rule out other medical disorders, intoxication, withdrawal syndromes, caffeine use, and complications of medication use

Treatment

- Panic disorder is highly treatable; as many as 85% of patients who complete a combination of medication and psychotherapy will improve
- Patient education regarding the diagnosis and its implications is crucial because many patients feel as if they are going to die during an attack and are concerned that they have a serious medical disorder

Psychotherapy

- Cognitive-behavioral therapy is equivalent to pharmacotherapy and may be more efficacious for preventing relapse. After therapy is finished, patients can continue to use the techniques and concepts they have integrated to prevent symptoms; patients who have finished pharmacotherapy do not have this resource
- A combination of therapy and medication is probably better than medication alone

*Panic disorder treated with cognitive-behavioral therapy (CBT) and/or antidepressants: response rates**

Treatment period	Patients maintaining 40% reduction in symptoms, %	Dropout rate in each phase, %
Acute phase (1st 12 wk)		
CBT alone	49	25
Imipramine alone	46	39
CBT and imipramine	60	28
Placebo	22	42
Maintenance phase (next 26 wk)		
CBT alone	40	17
Imipramine alone	38	17
CBT and imipramine	57	10
Placebo	13	67

*From Barlow et al.[11]

Pharmacotherapy

- Selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), venlafaxine, nefazodone, and benzodiazepines (alprazolam and clonazepam) are all effective treatments
- SSRIs and TCAs may take 3 to 6 weeks to induce a response
- Benzodiazepines are immediately effective in treating anticipatory anxiety and phobic avoidance. Drawbacks include many adverse effects and the potential for dependence and abuse
- It may be reasonable to give a benzodiazepine for 4 to 6 weeks until the patient shows an adequate response to an antidepressant agent
- The medication regimen should continue for at least 6 months before a dosage taper is attempted

Elements of cognitive-behavioral therapy for panic disorder
- Patient education
- Monitoring of panic symptoms
- Breathing techniques
- Cognitive change of catastrophic thoughts associated with panic attacks
- Exposure and desensitization to somatic fear cues

Glass RM. Panic disorder—it's real and it's treatable. JAMA 2000;283:2573-2574.

[11] *Barlow DH, Gorman J, Shear MK, Woods S. Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: a randomized controlled trial. JAMA 2000;283:2529-2536.* A double-blind RCT of 312 patients. The acute phase consisted of eleven 50-minute therapy sessions and/or 30-minute drug treatment sessions over 12 weeks. The maintenance phase included only treatment responders, they had similar sessions every month for 6 months. Differences between cognitive-behavioral therapy and imipramine were not statistically significant. All differences with placebo were significant.

Alprazolam is short acting and therefore may cause rebound anxiety between doses. It also causes drug dependence more often than clonazepam.

*TCAs, SSRIs, and placebo in the treatment of panic disorder percentage of patients (%) with no further full panic attacks**

Agent	Week of follow-up 3	6	9	12
Clomipramine	8	30	37	50†
Paroxetine	8	36†	51†	51†
Placebo	8	24	32	33

In 2 additional years of follow-up, 85% of patients who took paroxetine achieved success compared with 72% of patients who took clomipramine and 59% of patients who took placebo (from Lecrubier et al[12,13]).
†$P < 0.05$ for drug versus placebo.

[12] *Lecrubier Y, Bakker A, Dunbar G, Judge R, and the Collaborative Paroxetine Panic Study Investigators. A comparison of paroxetine, clomipramine and placebo in the treatment of panic disorder. Acta Psychiatr Scand 1997;95:145-152.* A double-blind RCT of 367 patients with panic disorder.

[13] *Lecrubier Y, Judge R and the Collaborative Paroxetine Panic Study Investigators. Long-term evaluation of paroxetine, clomipramine and placebo in panic disorder. Acta Psychiatr Scand 1997;95:153-160.* This study included patients from the above study who completed the 12-week course of therapy and elected to continue receiving their randomized treatments (ie, a self-selected group).

Drugs for depression, anxiety, and somatization†*

Drug	Dosage forms	Usual dose	Dose range	Comments
Benzodiazepines				
Alprazolam (Xanax)	0.25/0.5/1.0/2.0 mg	0.25-1.5 tid		Elimination half-life: 6 to 20 hr; alprazolam, 0.5 mg orally, is equivalent in potency to lorazepam, 1 mg
Lorazepam (Ativan)	0.5/1.0/2.0 mg	1 bid-2 tid		Elimination half-life: 10-20 hr
Diazepam (Valium)	2/5/10 mg	2 bid-10 qid		Rapid onset of action; elimination half-life: 30 to 100 hr; diazepam, 5 mg orally, is equivalent in potency to lorazepam, 1 mg
Chlordiazepoxide HCl (Librium)	5/10/25 mg	5 tid-10 qid		Elimination half-life: 30 to 100 hr; chlordiazepoxide, 10 mg, is equivalent in potency to lorazepam, 1 mg
Clonazepam (Klonopin)	0.5/1.0/2.0 mg	0.25-2.0 tid		Elimination half-life: 18 to 50 hr; clonazepam, 0.25 mg, is equivalent in potency to lorazepam, 1 mg
Flurazepam HCl (Dalmane)	15/30 mg	15-30 mg a day		Elimination half-life: 50 to 100 hr for the major metabolite
SSRIs				
Fluoxetine HCl (Prozac)	10/20 mg tablets; 20 mg/5 mL liquid	20 mg a day	5-80 mg a day	Most common side effects: diarrhea, headache, nausea, insomnia, anxiety, decreased libido, delayed ejaculation, anorgasmia; give half lowest usual dose for 7 days, then titrate up to ususal dose
Sertraline HCl (Zoloft)	50/100 mg	100-150 mg a day	50-200 mg a day	Same as above
Paroxetine (Paxil)	20/30 mg	20 mg a day	10-50 mg a day	Same as above
Citalopram hydrobromide (Celexa)	20/40 mg	20-40 mg a day		Same as above
TCAs				
Desipramine HCl (Norpramin)	10/25/50/75/ 100/150 mg	150-200 mg at bedtime	25-300 mg at bedtime	Start at a low dose and titrate until therapeutic range achieved; increase every 4 wk; less sedating than tertiary amines; common side effects: blurred vision, constipation, dizziness, dry mouth, tremors, and urinary disturbance
Imipramine HCl (Toframil)	10/25/50/75/ 100/125/150 mg tablets	150-200 mg at bedtime	50-300 mg at bedtime	Same as above
Other antidepressants				
Bupropion HCl (Wellbutrin)	75/100 mg tablets	100 mg bid for 7 days, then 100-150 mg tid		Side effects: anxiety, restlessness, insomnia Does not cause sexual dysfunction
(Wellbutrin SR)	100/150 mg	150 mg a day for 7 days, then 150-200 mg bid		The incidence of seizures is 0.4%, slightly higher than with other antidepressants
Venlafaxine (Effexor)	25/37.5/50/75/ 100 mg	75-225 mg a day; divide into a bid schedule	75-450 mg a day	Same side effects as SSRIs; may also cause sedation, sweating, and at high doses, increased blood pressure
(Effexor XR)	37.5/75/100 mg	75-225 mg daily		Same as above; XR form is taken once a day
Trazodone HCl (Desyrel)	50/100/150/ 300 mg	200-300 mg at bedtime	30-600 mg a day	Dosage for depression. Side effects: sedation, orthostatic hypotension, nausea, emesis
Other anxiolytics				
Buspirone HCl (BuSpar)	5/10/15 mg	5-10 tid; can be given bid		Does not cause sedation, may cause restlessness; headache, gastrointestinal effects, and dizziness occur rarely; not highly toxic in overdose

tid = 3 times a day; PO = by mouth; bid = twice a day; qid = 4 times a day; HCl = hydrochloride.
*Adapted from *Arana GW, Rosenbaum JF. Handbook of Psychiatric Drug Therapy. Philadelphia, PA: Williams & Wilkins; 2000.*
†Trade names are given (in parentheses) for information only and are not to be construed as endorsement by the authors or the editors of this journal.